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EXAMINER
SHARAREH, SHAHNAM J

ART UNIT	PAPER NUMBER
1619	20

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/351,862	Applicant(s) THORPE ET AL.	
	Examiner Shahnam Sharareh	Art Unit 1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *28 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30 and 34-42* is/are pending in the application.

4a) Of the above claim(s) *2,13,15-18,30,37 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-12,14,19-29,34,35 and 39-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *2,13,15-18,30,37 and 38* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Amendment filed on September 28 Paper No. 14 has been entered. Claims 1-30, 34-42 are pending.

2. Claims 2, 13, 15-18, 30, 37-38 are withdrawn from further consideration, as being drawn to a nonelected species. Applicant timely traversed the restriction (election) requirement in Paper No. 14. Claims 1-30, 34-42 are pending, however, claims 1, 3-12, 14, 19-29, 34-35, 39-42 are under consideration at this time.

3. This application contains claim 2, 13, 15-18, 30, 37-38 drawn to an invention nonelected with traverse in Paper No. 14. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP. 821.01. Claim 15 was inadvertently included in the previous rejections but it was never searched. Accordingly, it is withdrawn from further consideration.

Response to Amendment

4. Applicant's argument with respect to the rejection of claims under 35 USC 112 first and second paragraph have been fully considered and are found partially persuasive. Accordingly, any rejection that is not addressed in this Office Action is considered withdrawn.

5. The Declaration filed on September 20, 2001 under 37 CFR 1.131 is sufficient to overcome the WO 98/29453 reference. Accordingly, the rejections of claims under 35 U.S.C. 103(a) have been obviated.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-12, 14-15, 19-29, 34-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. The recitation of "at least a second anti-cancer agent" in claims 1, 22-23, 34 and their dependent claims, is ambiguous. Applicant's arguments with respect to this rejection have been fully considered but they are not persuasive.

8. Applicant argues that the recitation must be interpreted in light of the specification and that in light of the present disclosure, it is clearly understood that "first" anti-cancer agent is "the first antibody, or an antigen binding fragment thereof, that binds to an aminophospholipid." Applicant further contends that there are incredibly detailed teachings concerning the use of naked anti-aminophosphlipid antibody as the first anti-cancer agent.

9. In response, Examiner states that first of all the instant claims are not directed to "naked anti-aminophospholipid antibodies", nor are they reciting the term "the first anti-cancer agents" as described in specification at page 32, lines 1-9. Rather the claims are directed to a first antibody, or an antigen binding fragment thereof, and a detectably labeled antibody, or antigen-binding fragment thereof that binds to an aminophospholipid or at least a second anti-cancer agent.

Therefore, there is no indication as to what encompasses the first anti-cancer agent?

10. Second, even in light of the specification at page 32, line 1-9, the claims are ambiguous. The specification at page 32, line 6-7 of the states "'The at least a first cancer agent' may thus be considered to be 'at least a second anti-cancer agent'." This definition does not clarify the ambiguities of the rejected claims. Accordingly, even in view of the specification the metes and bounds of the claim are not clear.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

12. Claims 1, 3-6, 8, 12, 14, 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Fishman (IDS, 2/14/2000).

The instant claims are directed to a kit comprising a biologically effective amount of first antibody that binds to an aminophospholipid, and an anticancer agent.

13. Fishman discloses anti-phospholipid antibodies directed to melanoma cells and other the cancer cells having over expressed outer membrane phosphatidylserine (abstract). Fishman discloses purifying IgG anti-PS antibodies from patients with antiphospholipid syndrome and examining their *in vivo* efficacy against melanoma tumor cells ELISA tests (see page 903, 1st col, 2nd paragraph).

14. As argued in Applicant's Response filed on September 28, 2001 and further in view of the definition of 'at least the second anti-cancer agent' at page 32, line 1-9, it appears that the second anti-cancer agent can be the same as the first anti-cancer agent. Moreover, the first anti-cancer agent encompass anti-aminophospholipid antibodies (see instant specification page 32, lines 1-9), thus, it is Examiner's position that Fishman's separate doses of anti-PS antibodies meets the limitations of the instant claims because they are directed to two separate anti-cancer agents. Furthermore, Fishman teaches the potential use of autoantibodies in diagnostic and therapeutic area such as treatment of squamous cell carcinoma of the skin (abstract, page 903, 2nd col, 2nd paragraph). Accordingly, Fishman's teachings anticipate the limitations of the instant claims.

15. Claims 1, 3-12, 14, 19-22, 39-42 are rejected under 35 U.S.C. 102(e) as being anticipated by Schroit US Patent 6,300,308.

Schroit discloses methods for inhibiting cancer cell growth or killing cancer cells comprising eliciting a lipid specific antibody response with an immuologically effective amount of composition comprising a phophatidylserine/polypetptide conjugate (abstract; col 13, lines 44-49; col 32, lines 50-60). Schroit further discloses kits comprising a lipid or lipid-carrier conjugate antigen-specific antibodies with suitable immunodetecting reagents such as detectable labels linked to a protein, peptide or antibody directed to aminophospholipid receptors in suitable pharmaceutical formulations (col 6, lines 65-68; col 7, lines 13-35; example; col 23, lines 29-65). Furthermore, Schroit sets forth that his PS-specific antibodies can be used in for prevention and treatment of conditions such as cancer wherein surfaces of the cells causing the condition are characterized by the presence of PS on their external leaflet (col 16, lines 38-44; col 19, lines 36-67).

16. Schroit also discloses therapeutic kits comprising one or more lipid-conjugate antigens or antibodies directed to phosphatidylserine receptors in separate containers (col 7, lines 40-67; col 8, lines 1-40; col 28, lines 1-67); subsequently, the kits of Schroit contain at least two anticancer agents. Moreover, Schroit teaches combination of his antibodies with a secondary anti cancer agents such as diphtheria toxoid (col 8, lines 65-67). Finally, Schroit discloses the use of humanized antibodies or recombinant antibodies in preparing his compositions (col 4, lines 33-49; col 13, lines 25-55). Furthermore, the priority date of Schroit is earlier than the effective filing date of the instant application. Accordingly, Schroit is a competent prior art and anticipates the limitations of the instant claims.

R jections - 35 USC 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 23-29, 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schroit US Patent 6,300,308 in view of Gimbrone US Patent 5,632,991 and Umeda (IDS, 9/19/1999).

The teachings of Schroit are discussed above. Schroit teaches that various known techniques may be used to prepare more specific antibodies. Further, Schroit elaborates that various types of antibodies such as humanized mAbs, or murine modified antibodies may be used for his methods (see col 4, lines 38-49; col 13, lines 24-55). Schroit, however, fails to specifically disclose the use of other

suitable antiphospholipid antibodies in combination with a second anticancer agent conjugated with a targeting antibody.

19. Gimbrone discloses targeting agents conjugated to an antibody directed to ELAM-1 (E-Selectin), (col 5, lines 18-38). Gimbrone teaches that such endothelial specific adhesion molecules are rapidly unregulated on the surface of cultured human vascular endothelial cells (col 27, lines 59-67). Gimbrone also discloses the use of his targeting agent-therapeutic agent conjugate, alone or in combination with other antibody or antibody fragment and/or a therapeutic agent (a second anti-cancer agent) (col 15, lines 46-55). Therapeutic agents of Gimbrone produce apoptosis as they encompass various toxins, antioxidants and anti-tumor drugs (see col 12-14, claim 2). Finally Gimbrone teaches that E-Selectin or a leukocyte-binding fragment thereof can be coupled to a chemotherapeutic drug that binds to tumor cell expressing receptors for E-Selectin, to kill the tumor cell (col 13, lines 58-67). Gimbrone also disclose methods for detecting E-Selectin expression within the body of a patient comprising steps of detecting E-Selectin by labeling the E-Selectin antibody with a radioactive isotope that can be detected under a scintillation counter (col 18, lines 60-65). Gimbrone does not teach the combination therapy of his antibody-therapeutic agent conjugate with an anti-aminophospholipids antibody.

20. Umeda teaches methods of producing monoclonal antibodies directed to phosphatidylserine of plasma membrane, and that patients with malignancy have a higher titer of anti-PS antibodies (see abstract, page 2273; 2nd col, 2nd

paragraph, 2276). Umeda's teachings are used to show the conventional practice of preparing monoclonal antibodies directed to phosphatidylserine of outer cell membrane. Umeda does not teach the use of his antibodies in kits for diagnostic or therapeutic purposes.

21. The teachings of Schroit, Gimbrone and Umeda are in the same field of endeavor as they are all directed to the field of antibody immunology.

It is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In *re Kerkhoven*, 205 USPQ 1069(CCPA) 1980.

22. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to combine the antiphospholipid antibodies of Schroit with conjugates of Gimbrone in the same or distinct compositions, because the idea of combining them flows logically from their having been individually taught in prior art. Therefore, the claims that require no more than mixing together two conventional anti-tumor agents set forth prima facie obvious subject matter. Furthermore, as Umeda teaches that preparing monoclonal antibodies directed to aminophospholipids are conventional. Thus as suggested by Schroit, one of ordinary skill in the art would have had a reasonable expectation of success in using various forms of antiphospholipid antibodies such as monoclonal forms to prepare more specific therapeutic agents directed to the receptor sites of interest.

23. Claims 7, 9-11, 20-29, 34-35, 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman (IDS 2/14/2000) in view of Newman et al US Patent 5,658,570, as applied to claims 7, 9-11, 20-22 and further in view of Gimbrone US Patent 5,632,991 (IDS, 9/19/1999) as applied to claims 23-29, 34-35, 39-42.

24. Fishman discloses anti-phospholipid antibodies directed to melanoma cells and other the cancer cells having over expressed outer membrane phospatidylserine (abstract). Fishman discloses purification of IgG anti-PS antibodies from patients with antiphospholipid syndrome and examining their *in vivo* efficacy against melanoma tumor cells by an ELISA test (see page 903, 1st col, 2nd paragraph). Fishman fails to show the use humanized or other suitable antibodies in combination with an anticancer agent conjugated to a targeting antibody.

25. Newman et al teaches methods of preparing humanized antibodies directed to human receptor antigens such as ELAM, VCAM, TGFα, etc.. (see abstract, col 35, lines 1-54, col 11-16) for therapeutic administration (col 24-26). Accordingly, preparing such forms of antibodies is conventional. Newman's methods improves immunological limitations associated with human antibodies in a clinical settings (see col 2, lines 45-65). Newman does not teach humanized antibodies directed to cell surface aminophosphlipids.

26. The teachings of Gimbrone are discussed above.

27. The teachings of Fishman, Newman, and Gimbrone are in the same field of endeavor as they are all directed to the field of antibody immunology.

28. Accordingly, although Fishman does not specifically teach the use of humanized antibodies in his methods, it would have been obvious to one of ordinary skill in the art at the time of invention to prepare humanized form of Fishman's antibodies by methods of Newman, because the ordinary skill in the art would have had a reasonable expectation of success in improving specificity while minimizing antigencity of Fishman's antibodies.

29. Furthermore, it would have been obvious to one of ordinary skill in the art at the time of invention to combine the antiphospholipid antibodies of Fishman or its humanized counterparts with conjugates of Gimbrone in the same or distinct compositions, because the idea of combining two types of compositions used for the same purpose flows logically from them having been individually taught in prior art. Therefore, the claims that require no more than mixing together two conventional anti-tumor agents set forth prima facie obvious subject matter.

Conclusion

30. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh, PharmD whose telephone number is (703) 306-5400. The examiner can normally be reached on Monday to Friday from 8:30 a.m. to 5:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Diana Dudash can be reached on 703-308-2328. The fax phone number for this Group

is 703-308-4556. Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is 703-308-1235.

Shahnam Sharareh, PharmD
Patent Examiner, Art Unit 1619

ss 12/5/2001